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Perspectives

Potential role of autofluorescence imaging in determining biopsy of oral potentially malignant disorders: A large prospective diagnostic study

Linjun Shi[a,1], Chenxi Li[a,1], Xuemin Shen[a], Zengtong Zhou[a], Wei Liu[b,*], Guoyao Tang[a,*]

[a] Department of Oral Mucosal Diseases, Shanghai Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine, National Clinical Research Center for Oral Diseases, Shanghai Key Laboratory of Stomatology & Shanghai Research Institute of Stomatology, Shanghai, China
[b] Department of Oral and Maxillofacial-Head and Neck Oncology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

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ABSTRACT

Autofluorescence examination of oral tissues using the VELscope has been suggested as an adjunctive tool for cancer detection and diagnosis. This study aimed to determine the diagnostic value of VELscope in a large prospective study of 517 patients with oral potentially malignant disorders (OPMD). For the outcome assessments of discrimination of carcinoma form general OPMD and distinguishing high-risk lesions (moderate/severe dysplasia and carcinoma) from low-risk lesions (no/mild dysplasia), high sensitivity (100% and 95.9% respectively) and negative predictive value (100% and 98.2% respectively) were observed. All the carcinoma and showed loss of autofluorescence (LAF) and only 3 (0.6%) moderate/severe dysplasia were observed without LAF.

These data indicate that the cases without LAF using VELscope substantially rule out the presence of high-risk lesions including cancer. This may prove to be useful specially to alleviate patient anxiety regarding a clinically suspicious oral lesion without the LAF, and to avoid a unnecessary biopsy for these cases. Collectively, a perspective to highlight was that a no biopsy strategy may be appropriate for OPMD without LAF using VELscope after conventional oral examination.

Introduction

Oral squamous cell carcinoma (OSCC) is one of the leading causes of cancer death in the world. It is typically preceded by oral potentially malignant disorders (OPMD), a recognizable group of clinically suspicious lesions, that have a risk of progressing to SCC [1]. Although the majority of general OPMD do not progress to cancer, distinguishing high-risk lesions from low-risk lesions is crucial for preventing cancer progression and improving survival rates [2]. Currently, conventional oral examination (COE) and scalpel biopsy remain the gold standard for diagnosis of OPMD and OSCC; however, there are some limitations such as time-consuming, resource requirements, and sampling bias that can lead to underdiagnosis or misdiagnosis [3]. It is a promising technology that adjuncts for the detection of high-risk changes not apparent with white-light visualization have the potential value to guide the management of patients with OPMD [4].

As a result, several non-invasive diagnostic adjuncts, including autofluorescence imaging, have been developed with the aim to aid in the early detection of oral cancer, which may help practitioners better evaluate OPMD before definitive biopsy [5]. In particular, VELscope as an autofluorescence device for oral cancer screening has been investigated by various studies with diverse conclusions [6]. Recently, the diagnostic values of autofluorescence devices including VELscope were well reviewed by Mascitti et al. [7] and Tiwari et al. [8]. Particularly, these results must be interpreted prudently due to heterogeneity and some reasons: small sample size, different inclusion and exclusion criteria for the participating subjects, different study designs including prospective or retrospective cohort and cross-sectional studies, a general dental or specialist practitioner setting [7–9]. Overall poor specificity was reported along with significant heterogeneity in prior studies, and this weakness of VELscope always limits clinical use in routine general practice [7,8]. Besides, these studies were performed in various populations and countries such as USA, Canada, UK, Italy, Iran and India [10].

Given the various discrepancies on the diagnostic value of the VELscope, and the fact that the application of this device is not reported in mainland of China, this study thus aimed to determine the diagnostic value in three outcome assessment: (i) detection of dysplasia and OSCC in general OPMD; (ii) discrimination of OSCC form general OPMD; (iii) distinguishing high-risk lesions (moderate/severe dysplasia and OSCC)

* Corresponding authors.
E-mail addresses: liuweb@hotmail.com (W. Liu), tanggy@shsmu.edu.cn (G. Tang).
[1] LS and CL contributed equally to this work.

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from low-risk lesions (no/mild dysplasia) in a large prospective study from China.

Materials and methods

This study was approved by our local Institutional Review Board (SH9H-2016-79-T36) with written informed consent obtained from all participating subjects. Patients with oral white, red, mixed red and white lesions reporting to the Department of Oral Mucosal Diseases of our hospital from March 2016 to August 2018 were included in the current study. The patient, not being oral potentially malignant suspicious lesions but, with other oral mucosal diseases such as aphtha and pemphigus and tumor or tumor recurrence, as well as who had the history of treated cancer, was excluded in this study. A provisional clinical diagnosis of each subject was performed by oral medicine specialist after COE, followed by VELscope (LED Medical Diagnostics Inc, Burnaby, Canada) examination. A photograph documentation of each lesion during COE as well as the VELscope examination, was carried out for future review and correlation.

Based on the autofluorescence characteristics as determined by the manufacturer's instructions, the lesions were divided into two groups. Group LAF (loss of autofluorescence) included lesion that appeared dark compared to the surrounding unaltered tissue with pale green autofluorescence thus, indicating malignant or dysplastic change. Group RAF (retention of autofluorescence) included lesion that showed no change in autofluorescence when compared to the surrounding unaltered tissue thus, indicating no dysplastic change.

Each participant underwent biopsy. When the lesion with retention of AF using VELscope, site selection for biopsy was based on white light; when the lesion with loss of AF, site selection was based on fluorescence of VELscope. The biopsy tissue was processed for routine histopathologic examination by two oral pathologists who were blinded each other to the VELscope findings and were not involved with the clinical arm of the study. The results of the VELscope examination results were compared to the histopathological diagnosis. As per the Ganga et al. [11] method, statistics including sensitivity, specificity, positive and negative predictive values (PPV and NPV) with 95% confidence interval (CI) were calculated to determine the diagnostic value of VELscope examination.

Results

According to selection criteria of patients with white, red, mixed red and white oral lesions, a total of 517 consecutive patients was enrolled in the prospective diagnostic study. There were 279 female and 238 male participants (ratio F: M = 1.17:1), and the average age was 51.9 years old (range, 22–85 years). There were 286 patients with clinical diagnosis of leukoplakia and 212 patients with diagnosis of lichen planus. The minority of the cases were erythroplakia, lichenoid reaction, hyperkeratosis and verrucous hyperplasia. The history of smoking and alcohol intake were observed in 29.4% and 20.9% cases, respectively.

VELscope examination of 517 patients revealed that 352 (68.1%) belonged to Group LAF whereas the remaining 165 (31.9%) belonged to Group RAF. Diagram of the COE, VELscope examination (Groups LAF and RAF), and histopathological results of all the patients is showed in Fig. 1. The COE, VELscope, and histopathological examination of a representative case of no dysplasia, moderate-severe dysplasia, and OSCC respectively are showed in Fig. 2.

On histopathological assessment, 186 (35.9%) of the 517 patients examined were with no dysplasia, 294 (56.9%) examined were with dysplasia, and the remaining 37 (7.2%) were malignant. Of these, 202 (39.1%) dysplasia and all 37 (7.2%) malignant lesions belonged to Group LAF, whereas 73 (14.1%) no dysplasia and 92 (17.8%) dysplasia belonged to Group RAF (Fig. 1). It is noteworthy that only 3 (0.6%) moderate/severe dysplasia belonged to Group RAF, and no case of OSCC showed RAF.

On comparison of the VELscope results with the histopathological diagnosis, the sensitivity, specificity, PPV and NPV of three outcome assessment, i) detection of dysplasia and SCC in oral suspicious lesions; ii) distinguishing high-risk lesions (moderate/severe dysplasia and OSCC) from low-risk lesions (no/mild dysplasia); as well as iii) discrimination of OSCC form oral suspicious lesions respectively were showed in Table 1. Notablely, the NPV of the diagnosis of high-risk lesions and OSCC was 98.2% (95%CI, 94.6–99.6%) and 100% respectively.

Discussion

VELscope (visually enhanced light scope) is a hand-held non-magnifying device for direct autofluorescence certified device, which is approved in 2006 by the US Food and Drug Administration as an adjunct to enhance the visualization of oral mucosal abnormalities [7]. To the best of our knowledge, the sample size (n = 517) of the current study was the largest one in a single study on the diagnostic value of the VELscope in oral cancer screening by a specialist practitioner setting form China. Strikingly, we for the first time determine the value in three outcome assessment: i) detection of dysplasia and OSCC in oral suspicious lesions; ii) discrimination of OSCC form oral suspicious lesions; iii) distinguishing high-risk lesions (moderate/severe dysplasia and OSCC) from low-risk lesions (no/mild dysplasia) in a prospective blinded study.

Although the diagnostic values of the VELscope were examined by various studies in various populations and countries, these results must be interpreted prudently with diverse conclusions (reviewed in Refs. [7,8]). First, small sample size was the ubiquitous one of main methodological errors in the large majority of the previous studies, since sample size is important to cancer screening [5,8]. The two latest reviews enrolled 32 studies on VELscope in oral lesions, but there were 21 (65.6%) studies with sample size < 100 and only two studies with sample size ≥ 200 [7,8]. One study enrolled 222 subjects was a general dental practitioner setting [12], and the other one study enrolled 200 subjects included 41 patients with clinical diagnosis of benign tumor such as granuloma and fibroma [11]. Secondly, different patient inclusion and exclusion criteria can influence both sensitivity and specificity. The efficacy of identification and risk assessment of OPMD can be increased after the exclusion of the non-OPMD cases [13]. Only patients with primary OSCC were enrolled in several studies (reviewed in Ref. [6]), and some subjects who had the history of treated OSCC also were enrolled in some studies (reviewed in Ref. [7]). Thirdly, cross-sectional study design was adopted by the more than half of studies [10,11], and a retrospective study was also reported recently [14]. Obviously, prospective blinded study has higher the level of evidence. Arguably, our prospective blinded study enrolled 517 subjects focusing on OPMD, consisted of patients with different clinical and histologic diagnoses. This population can be considered to be representative of the patient in a specialist practitioner's clinical practice. Hence, the results of this study could apply to the Clinic of Oral Medicine of various hospitals.

Sensitivity, specificity, PPV and NPV are calculated to determine the accuracy of VELscope examination analysis outcome. For the fist outcome assessment of detection of dysplasia and OSCC in oral suspicious lesions, the values of sensitivity, PPV and NPV were moderate (40%–75%) and specificity (< 40%) was low. For the second and third outcome assessments, poor PPV (< 20%) and low specificity (< 40%) were determined in discrimination of OSCC form oral suspicious lesions and distinguishing high-risk lesions from low-risk lesions. Indeed, the majority of the previous studies on patients with OPMD and/or OSCC reported low specificity value and low PPV, highlighting this is the primary diagnostic limitation of VELscope [7,8]. Given that poor PPV and low specificity, Velscope may be not a good adjunctive tool in the examination and follow-up treatment of high-risk lesions progressing to cancer. In our study, the relatively low specificity of the device led to a

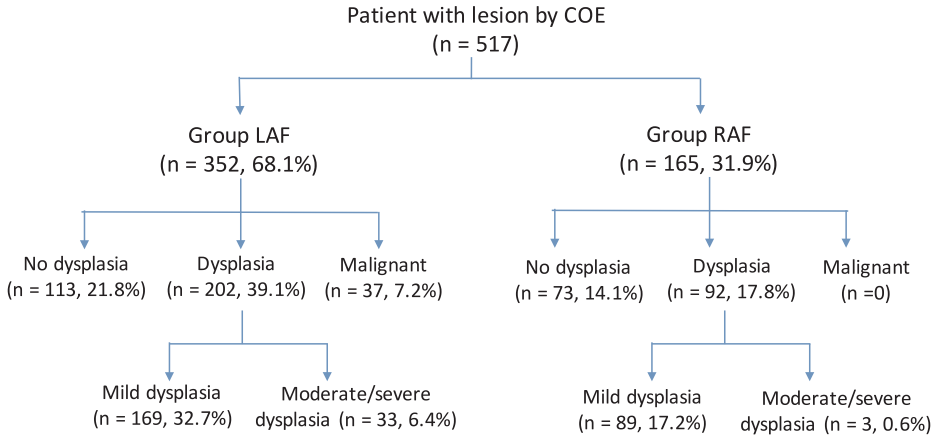

Fig. 1. Diagram of the conventional oral examination (COE), VELscope examination (Groups LAF and RAF), and histopathological results of the patients with oral potentially malignant lesion. LAF, loss of autofluorescence. RAF, retention of autofluorescence.

rather large number of false-positive test results (Table 1), which is not acceptable for clinical purposes. False-positive test results not only frighten patients but also increase morbidity risks because of unnecessary biopsy.

We determined that high NPV (100%) and sensitivity (100%) were in discrimination of OSCC form general OPMD, in line with a couple of the previous studies [11,15,16]. More importantly, high NPV (98.2%; 95%CI: 94.6–99.6%) and sensitivity (95.9%; 95%CI: 88.1–99.1%) were determined in distinguishing high-risk lesions from low-risk lesions. The relatively high sensitivity of the device led to a rather small number of false-positive test results (Table 1). It is noteworthy that only 3 (0.6%) moderate/severe dysplasia belonged to Group RAF, and no case of OSCC showed RAF. These findings indicate that the cases without the LAF using VELscope substantially rule out the presence of high-risk lesions including malignant event, which may contribute more to its effectiveness as an adjunct in a general practice setting. This may prove to be useful specially to alleviate patient anxiety regarding a clinically suspicious oral lesion without the LAF, and to avoid an unnecessary biopsy for these cases.

We are aware of the limitations of our study that the examination itself is of subjective, and adequate skill and training are required while interpreting the VELscope findings. Besides, the clinical practice of this

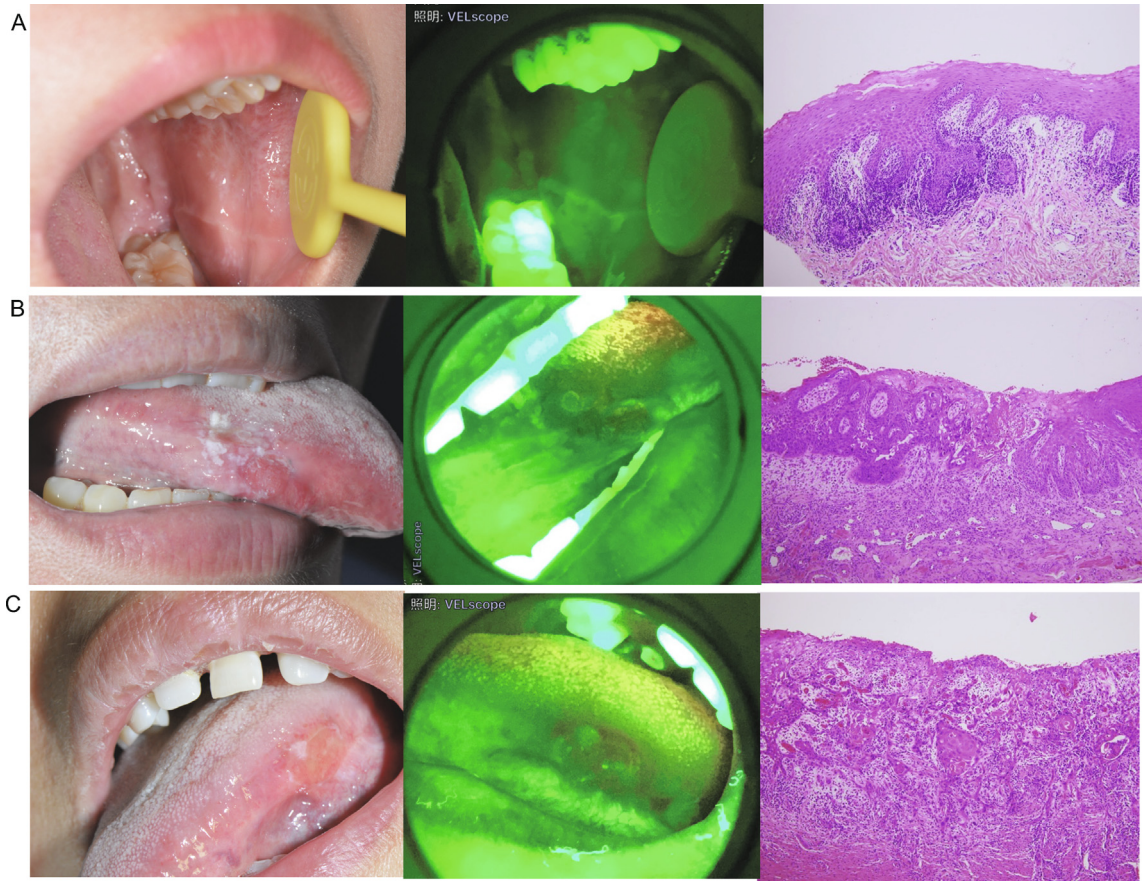

Fig. 2. The conventional oral examination, VELscope, and histopathological examination of a representative case. (A) No dysplasia with RAF, (B) moderate-severe dysplasia with LAF, and (C) carcinoma with LAF.

Table 1
Sensitivity, specificity, positive and negative predictive values (PPV and NPV) of the VELscope examination with 95% confidence interval (CI).

Group	Loss of AF (n = 352)	Retention of AF (n = 165)	Statistic % (95%)
Dysplasia + carcinoma No dysplasia	True positive (n = 239) False positive (n = 113)	False negative (n = 92) True negative (n = 73)	Sensitivity = 72.2% (67.1–76.8%) Specificity = 39.2% (32.5–46.4%) PPV = 67.9% (62.9–72.6%) NPV = 44.2% (36.1–51.9%)
Carcinoma OPMD with/no dysplasia	True positive (n = 37) False positive (n = 315)	False negative (n = 0) True negative (n = 165)	Sensitivity = 100% Specificity = 35.1% (30.9–39.1%) PPV = 10.5% (7.7–14.2%) NPV = 100%
High-risk lesion Low-risk lesion	True positive (n = 70) False positive (n = 282)	False negative (n = 3) True negative (n = 162)	Sensitivity = 95.9% (88.1–99.1%) Specificity = 36.5% (32.1–41.1%) PPV = 19.9% (16.0–24.4%) NPV = 98.2% (94.6–99.6%)

OPMD, oral potentially malignant disorder. AF, autofluorescence.

study is not a general provider setting but a specialist practitioner setting. Future studies should evaluate the subjectivity via an inter-observer agreement assessment. The use of quantitative analysis of autofluorescence developed to solve the problem of interobserver variability was promising [17]. Besides, the research on optimizing excision margin tissue in fluorescence image-guided surgery applications is warrant [18,19]. We also suggest that further prospective studies with adequate follow-up and clinical endpoints have to be conducted to evaluate the efficacy of the VELscope as a screening tool in oral cancer detection.

Conclusion

Our results of high sensitivity and low specificity indicate that VELscope examination could help to identify high-risk lesions, but cannot differentiate low-risk populations such as lichen planus from malignant lesions reliably. Tissue biopsy remains the gold standard for diagnosis of oral suspicious lesions [20]. VELscope examination may serve as an intermediate adjunctive tool between COE and a biopsy, and can not replace the COE in clinical practice. A perspective to highlight was that a no biopsy strategy may be appropriate for OPMD without loss of autofluorescence using VELscope after conventional oral examination. This as a temporary alternative strategy may prove to be especially useful to alleviate both patient and practitioner concerns regarding a clinically oral suspicious lesion.

Declaration of Competing Interest

None.

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